REMARKS

Claims 2, 9, 10, 17, 19, 20, 23, 25-32, 35, and 40-45 were pending in the instant application. Claim 2 has been amended to clarify Applicant's invention, and claims 46 and 47 have been added. Support for the amendment to claim 2 is found *inter alia* in the specification, for example, at page 17, line 11 to page 18, line 2. Support for new claim 46 can be found in the specification, for example, at page 17, lines 15 to 17. Support for new claim 47 can be found in the specification, for example, at page 9, lines 26 to 27. Thus, no new matter has been added. Upon entry of the above amendments, claims 2, 9, 10, 17, 19, 20, 23, 25-32, 35, and 40-47 will be pending.

1. The Rejection Under 35 U.S.C. § 102(e) Should Be Withdrawn

The Examiner has maintained the rejection of claims 2, 9, 10, 17, 19, 20, 23, 25-33, 35, 42 and 43 under 35 U.S.C. § 102(e) as allegedly anticipated by Li, U.S. Patent No. 6,984,389 ("Li"). In particular, The Examiner contends that because the instant claims do not specify the amount and the type of the peptides in the claimed α2M complexes, the complexes of Li appear to be the same as the claimed α2M complexes. Applicant respectfully submits that independent claim 2 as amended, and its dependent claims, are novel over Li for the reasons set forth below.

The legal standard for anticipation under 35 U.S.C. § 102 (b) is one of strict identity. A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987); *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). In other words, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). *See also, Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)(stating that the "identical invention must be shown in as complete detail as is contained in the patent claim").

Li does not anticipate independent claim 2 because Li does not teach each and every element of the claim. Specifically, Li does not teach the *in vitro* made complexes according to claim 2, in which the antigenic peptides of the complexes are derived from a protein preparation comprising total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of said type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction. Li teaches methods of treating cancer using α2M-peptide complexes. However, the complexes taught by Li are different from the complexes made according to the claims because the complexes of Li are either (1) endogenously (not *in vitro*) complexed, *i.e.*, the α2M and antigenic peptides are isolated already complexed with each other from antigenic cells or tissues (see *e.g.*, Li at col. 8, lines 15-23); or (2) complexed *in vitro* to specific peptides or proteins selected for their known immunogenicity or antigenicity (*i.e.*, known antigens, see *e.g.*, Li at col. 44-45, sec. 5.4.4), or to specific pools of peptides which have been selected from a protein preparation for their potential immunogenicity or antigenicity, *i.e.*, due to their ability to bind to stress proteins or MHC molecules (see *e.g.*, Li at col. 42, line 45 to col. 43 line 3, sec. 5.4.1, as well as cols. 43-44, sec. 5.4.2 (peptides from stress protein-peptide complexes), and sec. 5.4.3 (peptides from MHC-peptide complexes)).

The endogenous complexes of Li, which are isolated from cells or tissues, do not anticipate the complexes of claim 2, which are made *in vitro*, because the *in vitro* made complexes of the claimed invention would be expected to comprise different peptides than complexes purified from a cell or tissue. The pool of protease digested peptides used for complexing in claim 2 are from digests or cleavage of total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of said type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction. The pool of peptides available for complexing within a cell will not be identical to the digested or cleaved total cellular protein, total cytosolic protein, total membrane-bound protein, or total protein in a cellular fraction. Proteins and peptides are compartmentalized within a cell, thereby limiting the particular proteins and peptides available for complexing endogenously to α2M (see *e.g.*, by analogy to stress proteins, Applicant's specification at p. 10, lines 3-11). Thus, the complexes of the claimed invention will comprise a different population of peptides as compared to the

peptides found in the endogenous α2M complexes of Li, and as such, the complexes of the claimed invention are different from the endogenous complexes of Li.

The *in vitro* made complexes taught by Li do not anticipate the claimed complexes because the claimed complexes will comprise different peptides than the *in vitro* made complexes of Li. The *in vitro* made complexes taught by Li comprise either a specific peptide or protein (*i.e.*, a known antigen) or pools of peptides or proteins which have been selected for their potential immunogenicity or antigenicity based on their ability to bind to stress proteins or MHC molecules (see *e.g.*, Li at col. 46, lines 22-29, col. 42, line 63 to col. 43 line 3, and col. 44, lines 43-50). Assuming *arguendo* that protease digestion occurs during the complexing step of Li, what is complexed are digests of MHC-eluted or stress protein-eluted peptides. The claimed complexes, however, comprise peptides that are produced by digestion or cleavage of total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of said type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction. Thus, the pool of protease digested peptides used for complexing in claim 2 is not identical to the preselected digested antigen or digested hsp-eluted or digested MHC-eluted peptides used for complexing according to Li.

In view of the above, Applicant submits that Li fails to anticipate claim 2 or its dependent claims, 9, 10, 17, 19, 20, 23, 25-33 and 35, and respectfully requests that the Examiner's rejection under 35 U.S.C. § 102(e) be withdrawn.

2. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and the content of the prior art, the differences between the invention and the prior art, the level of the ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. *In re O'Farrell*, 853 F.2d 894, 902-4 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of

success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). In determining obviousness, "the inquiry is not whether each element existed in prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed." *Hartness Int'l Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 2 U.S.P.Q.2d 1826 (Fed. Cir. 1987). An analysis under 35 U.S.C. § 103(a) "should be made explicit," and "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1736 (2007), WL 1237834, at *14 and *15, respectively (2007).

The Rejection over Armen in view of Srivastava

The Examiner has maintained the rejection of claims 2, 9, 10, 17, 19, 20, 23, 25-33, and 40-43 under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 02/11669 ("Armen") in view of U.S. Patent No. 6,168,793 ("the Srivastava patent"). Applicant respectfully submits that claim 2, and its dependent claims, are patentable over Armen in view of the Srivastava patent for the reasons set forth below.

The complexes taught by Armen are different from and do not suggest the complexes made according to claim 2 because the complexes of Armen are either (1) endogenously (not *in vitro*) complexed, *i.e.*, the α2M and antigenic peptides are isolated already complexed with each other (see *e.g.*, Armen at Sec. 4.2.1, p. 20-22); or (2) complexed *in vitro* to specific peptides or proteins selected for their known or predicted immunogenicity or antigenicity (see *e.g.*, Armen at Sec. 4.2.1.1, p. 22-24; p. 30 lines 23-34; p. 32 lines 28-32; p. 33, lines 22-24). Both the endogenous and the *in vitro* made complexes produced according to Armen are different from the complexes produced according to claim 2 for the reasons discussed above in relation to Li.

As in Li, Armen uses a protease step for formation of the complexes (see e.g., Armen at p. 22 line 34 to p. 23 line 33), and not to produce a population of antigenic peptides for complexing according to claim 2. Even assuming *arguendo* that protease digestion occurs during the complexing step, Armen does not provide any reason that would have prompted a person of ordinary skill in the relevant field to use protease digestion to produce a population of peptides according to the method of claim 2 because, according to Armen, peptides (or proteins) are selected for complexing based on their antigenicity or immunogenicity (*i.e.*,

either they are known antigens or potential antigens based on their binding to stress proteins or MHC molecules, see *e.g.*, Armen at p. 30 lines 32-34 and p. 32 lines 28-32). Nowhere does Armen teach or suggest complexes comprising peptides that are produced by digestion or cleavage of total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of said type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction.

The deficiencies of Armen are not remedied by the Srivastava patent, which does not teach *in vitro* complexing, much less the use of proteases to produce peptides for such *in vitro* complexing methods. The Srivastava patent teaches the isolation of endogenous heat shock protein-peptide complexes from cells. The Srivastava patent does not teach or suggest complexes such as those made *in vitro* according to the method of claim 2. The differences between complexes made *in vitro* according to the claims and endogenous complexes isolated from cells are described above.

In view of the above, Applicant submits that Armen, combined with Srivastava, fails to render obvious claim 2, or its dependent claims 9, 10, 17, 19, 20, 23, 25-33, and 40-43, and respectfully requests that this rejection be withdrawn.

The Rejection over Li in view of Srivastava

The Examiner has rejected claims 2, 9, 10, 17, 19, 20, 23, 25-33, 35 and 40-45 under 35 U.S.C. § 103(a) as allegedly unpatentable over Li in view of U.S. Application Publication No. 2001/0034042 ("the Srivastava application"). Applicant respectfully submits that claim 2, and its dependent claims, are patentable over Li in view of the Srivastava application for the reasons set forth below.

As discussed above in response to the rejection under 35 U.S.C. § 102(e), Li does not teach or suggest complexes comprising peptides that are produced by digestion or cleavage of total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of said type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction, as required by claim 2.

The deficiencies of Li are not remedied by the Srivastava application which teaches complexes of heat shock protein fragments that are noncovalently associated with antigenic peptides (the Srivastava application at para. 88). The Srivastava application teaches chemical or enzymatic cleavage of heat shock proteins in order to obtain heat shock protein fragments for complexing to antigenic peptides (the Srivastava application at para. 192). Srivastava neither teaches nor suggests subjecting a protein preparation to digestion with one or more proteases or cleavage by one or more non-enzymatic methods to produce a population of antigenic peptides for complexing to alpha-2-macroglobulin, as required by claim 2. Accordingly, the Srivastava application, whether alone or in combination with Li, does not render obvious the complexes produced according to claim 2.

In view of the foregoing, Applicant submits that the rejection of claim 2, or its dependent claims 9, 10, 17, 19, 20, 23, 25-33, 35 and 40-45, under 35 U.S.C. § 103(a) is obviated and should be withdrawn.

3. The Obviousness-Type Double Patenting Rejections Should Be Withdrawn

The legal standard for an obviousness-type double patenting rejection requires a comparison of what is claimed in the earlier patent, not what was disclosed in the specification of the earlier patent. See *e.g.*, *General Foods, Inc. v. Studiengesellschaft Köhle mbH*, 972 F.2d 1272, 1280-81 (Fed. Cir. 1992). Although the specification may be used to determine the meaning of terms used in the claims, the specification may not be used as prior art. See *e.g.*, *In re Vogel*, 422 F.2d 438 (C.C.P.A. 1970).

The Rejection over U.S. Patent No. 6,984,389

The Examiner has maintained the rejection of claims 2, 9, 10, 17, 19, 20, 23, 25-33, and 35 over claims 48-50 of Li, U.S. Patent No. 6,984,389 ("the '389 patent") in view of the teachings of WO 02/11669 ("Armen") under the judicially created doctrine of obviousness-type double patenting. Applicant respectfully submits that claim 2 is not obvious over claims 48-50 of the '389 patent.

Claim 2 is not rendered obvious by claims 48-50 of the '389 patent because the claims of the '389 patent, which recite a "purified alpha-2-macroglobulin preparation" do not teach or suggest the *in vitro* made complexes according to claim 2. The endogenous complexes of

the '389 patent differ from the *in vitro* made complexes of claim 2 because the *in vitro* made complexes would be expected to comprise different peptides than complexes purified from tissue, for the reasons set forth above in the response to the rejections under 35 U.S.C. §§ 102(e) and 103(a). Nowhere does the '389 patent teach or suggest complexes comprising peptides that are produced by digestion or cleavage of total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of said type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction. The '389 patent does not provide any reason that would have prompted a person of ordinary skill in the relevant field to produce the *in vitro* made complexes according to claim 2.

The Examiner relies on Armen to remedy the deficiencies of the '389 patent by teaching *in vitro* made α2M complexes. However, as discussed above in response to the rejection under 35 U.S.C. § 103(a), Armen also does not teach or suggest the complexes specified in claim 2. The combined teachings of the '389 patent and Armen do not teach or suggest complexes comprising peptides that are produced by digestion or cleavage of total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of said type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction. As such, claims 48-50 of the '106 patent, in view of Armen, do not render obvious the method of claim 2.

In view of the above, Applicant submits that the rejection of claims 9, 10, 17, 19, 20, 23, 25-33, and 35, under the judicially created doctrine of obviousness-type double patenting is obviated and should be withdrawn.

The Provisional Rejection Over U.S. Patent Application No. 10/546,106

The Examiner also maintained the rejection of claims 2, 9, 10, 17, 19, 20, 23, 25-33, 35, and 40-43 over claims 2-4 and 8 of copending U.S. Patent Application No. 10/546,106 ("the '106 application") in view of the teachings of Armen under the judicially created doctrine of obviousness-type double patenting. Applicant respectfully submits that claim 2 is not rendered obvious by claims 2-4 and 8 of the '106 application.

Claim 2 is not rendered obvious by claims 2-4, and 8 of the '106 patent because the claims of the '106 application do not teach or suggest the *in vitro* made complexes according to claim 2. Claims 2-4 and 8 of the '106 application are directed to a method of treating

cancer comprising administering a complex of alpha (2) macroglobulin and antigenic molecule, wherein the complex was *isolated from a bodily fluid* of a mammal having cancer. The endogenous complexes of the '106 application differ from the *in vitro* made complexes of claim 2 because the peptides of complexes isolated from a bodily fluid will be substantially different from the peptides of the complexes made according to claim 2, which are produced by digestion or cleavage of total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of a type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction. The '389 patent does not provide any teaching or reason that would have prompted a person of ordinary skill in the relevant field to produce the *in vitro* made complexes according to claim 2.

Armen does not rectify these deficiencies of the claims of the '106 application, for the reasons discussed above, since it also does not teach complexes comprising peptides that are produced by digestion or cleavage of total cellular proteins, total cytosolic proteins, total membrane-bound proteins, or total protein in a cellular fraction, of cells of a type of cancer, wherein said cellular fraction is selected from the group consisting of a membrane fraction and an organelle fraction.

In view of the above, Applicant respectfully submits that claims 2-4 and 8 of the '106 application do not render obvious pending claims 2, 9, 10, 17, 19, 20, 23, 25-33, 35, and 40-43, and respectfully request that the Examiner withdraw this rejection.

CONCLUSION

Applicant believes that the present claims meet all of the requirements for patentability. Entry and consideration of the foregoing amendments and remarks into the file of the subject application are respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

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